REMARKS

In the present Office Communication, the Examiner has maintained Rejections under 35U.S.C. §§ 112, 101 and 103 that are considerably similar, if not identical, to rejections made in parent application 09/364,425 which was issued as US Patent No. 6,653,086 ("the '086 patent"). In Applicant's previous response, the claims were amended to conform to the structure of the claims of the '086 patent. In addition, arguments were presented for the patentability of the claims that mirrored those used to overcome these rejections during prosecution of the '086 patent (see the response filed by Applicants on November 8, 2001 during prosecution of the '086 patent).

In the remarks below, Applicants again reiterate the successful arguments made during prosecution of the '086 patent (and which were presented in Applicant's previous response). In addition Applicants provide evidence to rebut the Examiner's assertion that no orphan GPCRs had been associated with a disease or disorder at the time of filing the application.

In view of these remarks, Applicants respectfully request that the Examiner allow Claims 1-3, 8-10, 20 and 21, the only claims pending and under examination in this application.

REJECTIONS UNDER §112, ¶2

Claims 1-3 and 8-10, 20 and 21 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

In making this rejection, the Examiner asserts that Claim 1 and 12 are indefinite "because it is not clear what activity is measured since the activity of the orphan receptor is unknown and the associated G protein is unknown." (Office Action at page 3). Applicants note that Claim 12 was canceled in the previous amendment: Claim 1 is thus the only independent claim pending and under examination in this application.

As stated in MPEP §2173.02, "[t]he test for definiteness under 35 U.S.C. 112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986)."

As argued during prosecution of the '086 patent and reiterated in the previous response, the Applicants submit that one of skill in the art would understand what is claimed when read in light of the specification. The specification provides multiple exemplary assays for measuring the activity of a

GPCR (including an orphan GPCR), where the assay selected is based on the characteristics of the receptor under study.

The Examiner is again directed to page 33, lines 1-12, of U.S. Patent Application Number 09/060,188 ("the '188 application"), the entire disclosure of which is incorporated by reference in the present application (see page 1 of the present application) which states:

> A variety of second messenger screening assays can be employed to detect the receptor-mediated cellular response. The assay chosen primarily depends upon the type of receptor and the secondary pathway it activates. For example, for some G protein-coupled receptors an adenylyl cyclase activated system would provide the appropriate assay. For other G protein-coupled receptors, a phospholipase C linked assay would be appropriate. Appropriate assays for tyrosine kinase and other receptors are available and known to those skilled in the art. Preferred assays are summarized below. ***The assays of constitutively activated receptor activity not only demonstrate the functioning of the receptor activity, but they also provide a means to directly determine when the level of that activity has been decreased or increased. Thus, compounds which are inverse agonists would be expected to lower the observed basal level of activity while compounds which are agonists would be expected to increase the activity level above baseline.*** (emphasis added).

Further, the instant specification further describes several assays which can be utilized in connection with the claimed methods to determine whether a compound is an agonist or inverse agonist. For example, the specification discloses that [^{35}S]GTPγS assays (page 16) and cAMP detection assays (page 17) find use in practicing the claimed invention. By way of example, the instant specification states that "[A]ssays that detect cAMP can be utilized to determine if a candidate compound is an inverse agonist to the receptor (i.e., such a compound which contacts the receptor would decrease the levels of cAMP relative to the uncontacted receptor" (Specification, page 17).

Moreover, Applicants submit that numerous assays for measuring the activity of GPCRs were well known in the art at the time of filing the subject application.

Applicants conclude that, in keeping with the requirements for definiteness under §112, second paragraph, one of skill in the art would understand what is claimed when the claim is read in light of the specification.

In view of the foregoing arguments, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

REJECTIONS UNDER §101 AND §112, ¶ 1

Claims 1-3, 8-10, 20 and 21 were rejected under 35 U.S.C. §101 because the claimed invention is allegedly not supported by either a specific and substantial asserted utility or a well established utility.

In maintaining this rejection, the Examiner makes the following statements regarding arguments provided in the previous response:

> Although the method can identify agonist or inverse agonists of orphan receptors the method provides no patentable use for the agonists or inverse agonists since the receptor itself has no utility. Applicants and Dr. Watson argue that orphan receptors with no known ligand, but a known cellular function, such as the GPCR 19AJ or 18F have utility when used in the claimed method. If an orphan receptor such as GPCR 18F can be associated with a cellular function such as increasing or decreasing feeding behavior, or its presence or absence in the animal results in a lean or obese phenotype, then such a GPCRs when used in claimed method would have a utility. Based on the prior art no such orphan receptors are disclosed. Even though Applicants and Dr. Watson discuss GPCRs with no known ligand, but having a known cellular function, ***there is no disclosure that such orphan receptors were known at the time of filing of instant application.*** It is noted that none of the orphan receptors in claim 8 have a defined cellular function which would give them a patentable utility. (emphasis added)

In the excerpt above, the Examiner is asserting that prior to filing, ***no*** orphan GPCR had ***ever*** been associated with ***any*** disease or disorder, and as such, there is no utility to directly identify agonists/inverse agonists for any orphan GPCR as claimed. Applicants respectfully disagree.

As described in the previous response (and in detail during prosecution of the '086 patent), the third party references and the Watson Declaration makes clear that the functional role of an orphan receptor can be assessed and understood prior to identifying the receptor's endogenous ligand. Information that is relevant to revealing an orphan receptor's role include: where the receptor is expressed; the systems and circuits within which a receptor is located; how the receptor is expressed in normal versus disease state; and changes in receptor expression in response to certain conditions. This type of information can readily guide the skilled artisan to deduce the functional role of a receptor. Simply stated, drug discovery does not require the identification of a receptor's endogenous ligand as asserted by the Examiner.

In addition to this evidence, Applicants further submit that orphan receptors ***have*** been shown in the literature to be associated with diseases and disorders. Applicants submit herewith three different references evidencing this fact: (i) Liao et al., *The Journal of Experimental Medicine* (June 2, 1997) vol. 185, p. 2015-2023, entitled "STRL33, A Novel Chemokine Receptor–like Protein, Functions as a Fusion Cofactor for Both Macrophage-tropic and T Cell Line–tropic HIV-1"; (ii) Alkhatib et al., *Nature* (July 17, 1997) vol. 388, p. 238, entitled "A new SIV co-receptor, STRL33"; and (iii) Farzan et al., *The Journal of Experimental Medicine* (August 4, 1997) vol. 186, p. 405-411, entitled " Two Orphan Seven-Transmembrane Segment Receptors Which Are Expressed in CD4-positive Cells Support Simian Immunodeficiency Virus Infection".

Liao et al. describe the identification of a novel human gene, STRL33, which encodes an orphan GPCR having sequence similarity to chemokine receptors and to chemokine receptor–like orphan receptors. STRL33 is expressed in lymphoid tissues and activated T cells, and is induced in activated peripheral blood lymphocytes. In this reference, Liao et al. demonstrate that, in contrast with the major known cofactors CXCR4 and CCR5, STRL33 can function with CD4 to mediate fusion with cells bearing HIV-1 *Env* proteins from both T cell-tropic and macrophage-tropic HIV-1 strains. Therefore, Liao et al. disclose a human orphan GPCR associated with the infectivity and pathology of the virus that causes AIDS.

Alkhatib et al. describe further studies with the orphan receptor STRL33, this time in studies with simian immunodeficiency virus (SIV). Specifically, Alkhatib et al. show that transfection of STRL33 into Jurkat cells renders them competent for infection with SIV, demonstrating that this orphan receptor is a co-receptor for SIV. This activity has relevance to human AIDS apart from the general parallels between the human and simian systems, as SIV is phylogenetically thought to be the immediate progenitor of HIV-2, a virus known to cause AIDS in humans. Additionally, this study provides clues to understanding how individuals who are homozygous for an inactivating deletion in the CCR5 gene, and therefore thought to be resistant to HIV infection, are nonetheless infected with HIV-1. Specifically, HIV may rely on alternative co-receptors, including orphan receptors like STR33.

Farzan et al. disclose that two orphan seven-transmembrane receptors, gprl and gpr15, serve as coreceptors for SIV, and are expressed in human alveolar macrophages. Farzan et al. go on to find that gpr15 (the more efficient SIV coreceptor of these orphan receptors) is also expressed in human CD4 + T lymphocytes and activated rhesus macaque peripheral blood mononuclear cells. These results

underscore the potential diversity of seven-transmembrane receptors that are used as entry cofactors by primate immunodeficiency viruses, including orphan receptors gpr1 and gpr15.

Applicants therefore submit that, based on the evidence above, it is factually incorrect to assert that there are ***no*** examples of orphan receptors being associated with a condition or disease.

In the excerpt above, the Examiner has also stated that "the method provides no patentable use for the agonists or inverse agonists since the receptor itself has no utility". In essence, the Examiner is asserting that in the absence of Applicants delineating a patentable utility for ***each and every*** constitutively active orphan GPCR covered by the claimed methods, it has no patentable utility.

In response, Applicants submit that the utility of the claimed invention is similar to the utility of PCR. Specifically, the utility of PCR is not derived from the specific identity and utility of the polynucleotide being amplified, but rather from its ability to amplify virtually any polynucleotide ***of interest to a user*** (i.e., the utility of PCR is independent of the specific sequence or function of the nucleic acid being amplified). Similarly, the utility of the presently claimed invention is not derived from the specific identity and utility of the constitutively active orphan GPCR employed in the method, but rather from the ability of a user to employ the claimed methods to identify agonist/inverse agonist compounds for virtually any constitutively active orphan GPCR that is ***of interest to them***. As such, a user of the claimed invention of the instant application comes to the table with a constitutively active orphan GPCR ***of interest to them*** for which agonist/inverse agonist compounds are sought, and by practicing the claimed invention they can identify such compounds. Therefore, Applicants submit that, just as the utility of PCR is not derived from the specific identity and utility of the nucleic acid being amplified, the utility of the claimed invention is not derived from the specific identity and utility of the orphan GPCR deemed of interest by a user.

Applicants further submit that constitutively active orphan GPCRs have additional utility for use in the claimed screening assays as compared to non-constitutively active orphan GPCRs by virtue of the fact that both agonist and inverse agonist compounds can be identified for them without requiring that their natural ligands be known. In other words, constitutively active orphan GPCRs do not require stimulation with their natural ligand (which is not known) to place them in an activated state for use in the claimed assays.

With regard to the orphan receptors in Claim 8, Applicants note that the specification provides examples of pertinent features of certain of these receptors that could provide a basis for using them in the claimed assays. For example, GPR3 is shown in Example 7 to be more highly expressed in brain

tissue from subjects suffering from epilepsy (see, e.g., Figs. 7 and 8). In addition, Examples 8 and 9 show that the expression level of GPR6 affects feeding regulation in a model system (see, e.g., Figs. 9 and10).

However, Applicants again stress that it is ***the user of the claimed methods*** who determines which orphan GPCR to employ in the claimed methods based on their own criteria, not on any pre-conceived criteria supplied by Applicants and/or the prior art.

Brenner v. Manson

The Examiner again makes reference to the decision in *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966) as a basis for rejecting the claimed invention as lacking utility under 35 U.S.C. §101.

In the previous response, Applicants noted that a long line of well-grounded case law has established that under §101, the disclosure need merely provide an indication of usefulness of the invention. The threshold is so low under §101 that it is only when a claimed invention is totally incapable of achieving a useful result or incapable of serving any beneficial end that a rejection can properly be applied, and sustained, under §101. Thus, the following three words are dispositive to issues of utility under §101: Some. Identifiable. Benefit.

In addition to the arguments in the previous response, Applicants further submit that the claimed invention is not a "hunting license" as the court considered the Manson claims to be (and as asserted by the Examiner). Applicants remind the Examiner that the claims of the subject application do not specify a method for producing a compound having a particular structure with no well-established use, as did the Manson claims. Rather, the claimed invention is drawn to methods for identifying compounds, irrespective if their structure, that have a ***well-defined and useful activity***: i.e., agonist or inverse agonist activity for an orphan GPCR of interest to the user. Applicants contend that this is a material distinction, because by the very nature of the methods claimed in the subject application, the compounds identified find use as agonists or inverse agonists of the orphan GPCR of interest to the user. This is a specific, substantial and credible real-world use.

Thus, Applicants contend that the fact pattern of *Brenner v. Manson* and the claimed invention of the subject application are not interchangeable, and thus the court's decision that the claims of Manson did not meet the utility requirements of §101 cannot be applied without regard to this clear distinction.

In conclusion, the Applicants submit that the subject application fully discloses ***some identifiable benefit*** for the claimed invention, and thus meets (and exceeds) the requirements under 35 U.S.C. §101.

Indeed, the Applicants note that the claims of the present application conform to those of the '086 patent, the issued parent of the present application.

In view of the arguments above, the Applicants submit that the claimed invention clearly fulfills the utility requirements under 35 U.S.C. §101. Withdrawal of this rejection is thus respectfully requested.

REJECTIONS UNDER §112, ¶1

Claims 1-3, 8-10, 20 and 21 were rejected under 35 U.S.C. §112, first paragraph because the claimed invention is allegedly "not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Claims 1-3, 8-10, 20 and 21 were rejected under 35 U.S.C. §112, first paragraph solely because the claimed invention allegedly did not provide for a well-established utility nor a substantial utility. Because Applicants have established a well-established utility and a substantial utility that would constitute a real world use, one skilled in the art would clearly know how to use the claimed invention.

Therefore, Applicants respectfully request that this rejection also be withdrawn.

REJECTIONS UNDER §103(a)

Claims 1-3, 8-10, 20 and 21 were again rejected under 35 U.S.C. § 103(a) as allegedly obvious over Seifert et al. (J. Biol. Chem. 1998, Vol. 273, No. 9, 5109-51 16) in view of Scheer et al. (J. of Receptor and Signal Transduction Research, 1997, Vol. 17, 57-73) and further in view of Song et al. (Genomics, 1996, Vol. 28, 347-9), Bertin et al. (PNAS USA, 1994, Vol. 91, 8827-8831) and Wise et al. (J. Biol. Chem., 1997, Vol. 272, No. 39, 24673- 24678). Applicants respectfully traverse this rejection.

The Applicants note that the present §103 rejection is nearly identical to the §103 rejection presented by the Examiner in the previous Office Action. Applicants note that the amendments to the claims and the arguments employed to rebut this rejection mirrored those made during prosecution of the '086 patent (which were sufficient to overcome the rejection). However, the Examiner has failed to provide any further clarification of why the amendments and arguments are now considered non-persuasive. Without such clarification, Applicants have no guidance as to why the Examiner has maintained this rejection.

Therefore, the arguments presented below are largely duplicative of the previous arguments. Applicants respectfully request that the Examiner reconsider these arguments and, if found unpersuasive again, please provide the Applicants with comments directed to why the specific amendments and arguments, which were persuasive in the parent case, are now insufficient to overcome this rejection.

Deficiencies in Seifert, Scheer, Bertin, and Wise

Seifert is drawn to "Different Effects of Gsα Splice Variants on β2-Adrenoreceptor-mediated Signaling", and discusses the generation and testing of the β2-Adrenoreceptor coupled to splice variants of Gsα. The β2-Adrenoreceptor, although a G Protein Coupled-Receptor, is not an orphan G protein coupled cell surface receptor. Indeed, the endogenous ligand for the β2-Adrenoreceptor is known and the receptor has been characterized. As acknowledged by the Examiner, Seifert fails to teach or even suggest the claimed methods wherein the constitutively active G protein coupled receptor is an orphan receptor.

Also acknowledged by the Examiner is the fact that Seifert fails to teach or even disclose the particular orphan G protein coupled receptor -- e.g. GPR3, GPR4, GPR6, GPR12, GPR21, OGRI, GHSR, RE2 and AL022171.

In addition, Applicants emphasize that Siefert fails to teach identifying compounds as agonists or inverse agonists as claimed. Rather, Siefert employs known agonists and inverse agonists of the GPCR under study as a way to study differences in signaling from the different forms of the β2-Adrenoreceptor. In other words, Siefert does not teach or suggest a compound identification assay as claimed.

In keeping with this deficiency in Siefert, this reference also fails to teach or suggest the final candidate identification step recited in the claims as amended.

As its title indicates, the Scheer reference discusses "[t]he activation process of the α_{1B}-adrenergic receptor: Potential role of protonation and hydrophobicity of a highly conserved aspartate." However, ligands for the β2-Adrenoreceptor are known (see, for example, Table 1 of Scheer which discusses ligand binding properties of the adrenergic receptor), and the receptor has been characterized. Scheer fails to teach or even suggest the claimed methods wherein the constitutively active G protein coupled receptor is an orphan receptor.

Scheer also fails to teach or even disclose the particular orphan G protein coupled receptor -- e.g. GPR3, GPR4, GPR6, GPR12, GPR21, OGRI, GHSR, RE2 and AL022171.

Finally, Scheer fails to teach or suggest the final candidate identification step recited in the claims as amended.

As its title indicates, Bertin discusses the "[C]ellular signaling by an agonist-activated receptor/Gsα fusion protein", and discusses fusions of the β2-Adrenoreceptor/Gsα. As discussed in relation to the Seifert and Scheer references, ligands for the β2-Adrenoreceptor are known (see, page 8828 of Bertin which discusses the use of ICYP as a ligand), and the receptor has been characterized (see Table 1 and Figure 3 which set forth pharmacological properties of the receptor). Bertin fails to teach or even suggest the claimed methods wherein the constitutively active G protein coupled receptor is an orphan receptor.

In addition, Bertin also fails to teach or even disclose the particular G protein coupled receptor for which the endogenous ligand has not been identified -- e.g. GPR3, GPR4, GPR6, GPR12, GPR21, OGRI, GHSR, RE2 and AL022171.

Finally, Bertin also fails to teach or suggest the final candidate identification step recited in the claims as amended.

As its title indicates, the Wise reference discusses the "[R]ole of Functional Interactions between the α_{2a} -Adrenoreceptor and Acylation-resistant Forms of $G_{i1\alpha}$ by Expressing the Proteins from chimeric Open Reading Frames", and discusses fusions of α_{2a}-Adrenoreceptor and $G_{i1\alpha}$. However, ligands for the α_{2a} -Adrenoreceptor are known (see, page 24674 of Wise which discusses the use of RS-79948-197 as a ligand), and the α_{2a} -Adrenoreceptor has been characterized. Wise fails to teach or even suggest the claimed methods wherein the constitutively active G protein coupled receptor is an orphan receptor.

Further, Wise also fails to teach or even disclose the particular orphan G protein coupled receptor -- e.g. GPR3, GPR4, GPR6, GPR12, GPR2 1, OGRI, GHSR, RE2 and AL022171.

Finally, Wise fails to teach or suggest the final candidate identification step recited in the claims as amended.

Therefore, the combined teachings of Seifert, Scheer, Bertin, and Wise fail to teach or even suggest at least the following: 1) a method for directly identifying a non-endogenous candidate compound as an inverse agonist or an agonist, to an endogenous, constitutively active orphan GPCR, 2) particular orphan G protein coupled receptors (e.g. GPR3, GPR4, GPR6, GPR12, GPR21, OGRI, GHSR, RE2 and AL022171), and 3) the final candidate identification step recited in the claims as amended.

Song fails to Remedy the Deficiencies in Seifert, Scheer, Bertin, and Wise

The Song reference fails to remedy the deficiencies of Seifert, Scheer, Bertin and Wise, alone or taken in combination. Song fails to teach or even suggest a method for directly identifying a non-endogenous candidate compound as an inverse agonist or an agonist, to an endogenous, constitutively active orphan G protein coupled cell surface receptor. As its title indicates, the Song reference discusses the "Molecular Cloning and Chromosomal Localization of Human Genes Encoding Three Closely Related G Protein-Coupled Receptors", one of which is GPR6, an orphan GPCR.

However, Song fails to teach or suggest any method for identifying agonists or inverse agonists of a GPCR, less still a method for identifying agonists or inverse agonists of a constitutively active orphan GPCR.

In addition, Song also fails to teach or suggest the final candidate identification step recited in the claims as amended.

Therefore, the applicants submit that the combined teachings of the cited references fail to teach or suggest each and every limitation of the claimed invention.

The Examiner also asserts that one would be motivated to modify the teachings of Seifert, Scheer, Bertin and Wise with the teaching of Song (described by the Examiner as a constitutively active GPCR), to allegedly achieve Applicants' claimed invention, citing several passages from the cited references as alleged motivation for modifying the teachings of the same.

However, none of the cited passages contains any disclosure or suggestion whatsoever to apply the disclosure of methods relating to GPCRs with known ligands to orphan GPCRs. Indeed, none of the quotations provided by the Examiner refer to orphan receptors at all, and Applicants are unable to locate any reference to orphan receptors in any of Seifert, Scheer, Bertin and Wise.

Further, the Song reference fails to teach or suggest any method for identifying agonists or inverse agonists of a GPCR. Thus, in addition to a lack of legally sufficient reason to combine the teachings of the cited art, even when so combined the combination would not teach Applicants' invention as presently claimed. Prior to Applicants' invention, there was no teaching in the art that constitutively active orphan G Protein-Coupled Receptors were useful for determining agonists and inverse agonists of the receptor. Rather, prior research involving orphan GPCRs was focused on identifying the ligand of the receptor, often using homology to receptors with known ligands as a guide. The prevailing wisdom in the GPCR field was that the determination of agonists or antagonists of a GPCR was an activity that invariably happened after the ligand was identified.

Accordingly, the skilled artisan had no reason to combine the teachings of Seifert, Scheer, Bertin and Wise with the teachings of Song. Indeed, the only source of such motivation is Applicants' own disclosure, and, as has been invariably held by the Courts, the use of an Applicant's specification as reason to combine or modify references in an obviousness analysis is not permissible.

In view of the discussion above, it is clear that the Examiner has failed to establish a *prima facie* case of obviousness for the claimed invention. Indeed, this same rejection was successfully traversed by the Applicants in the '086 patent, which claims similar subject matter.

Therefore, because the Examiner has failed to provide a legally sufficient reason to combine the teachings of references as asserted in the Office Action, and because such combination would not result in Applicants' claimed invention, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number AREN-005CON.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: July 23, 2008

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Enclosure(s): (i) Liao et al., *JEM* (June 2, 1997) vol. 185, p. 2015-2023;
(ii) Alkhatib et al., *Nature* (July 17, 1997) vol. 388, p. 238;
(iii) Farzan et al., *JEM* (August 4, 1997) vol. 186, p. 405-411

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